

Figure 1



1

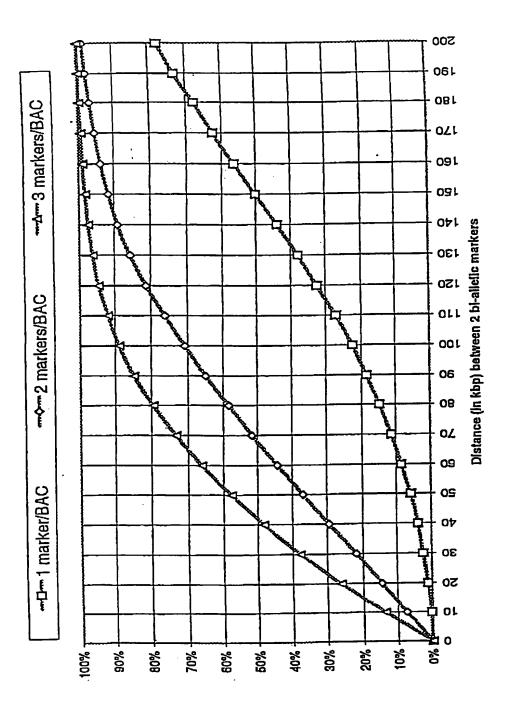
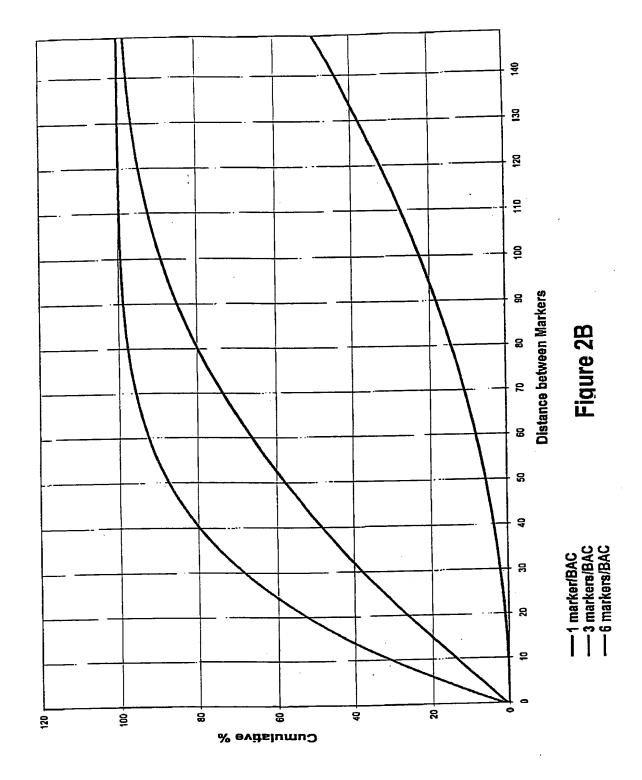


Figure 2A

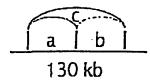






LD in a random French caucasian population

- 54 sized « random » BACs covering 8100 kb
- 213 SNP; 2 to 6 / BAC, mean allele frequency = 0.3
- Order and distance unknown
- For 1 BAC:



- * \overline{m} intermarker distance : 130/3 = 43 kb
- * \overline{m} LD strength estimate: m (a,b,c) = 0.51
- For 54 BACs:
- * m intermarker distance = 38 kb
- * \overline{m} LD strength estimate = 0.63 ± 0.05 (324 pairs)
- For 19 unlinked SNPs: m LD strength estimate = 0.12 ± 0.007 (171 pairs)



p-VALUE DISTRIBUTION

# aff	150						
# non aff	150						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
ΔpAi	0,05	8,77E-05	8,77E-05 0,06407752		0,14252002 0,19106311 0,21543442 0,22009395	0,21543442	0,22009395
ΔpAi	0,1	1,91E-08	0,00060364	0,00467774	0,01023571 0,01382303	0,01382303	0,01382303
ΔpAi	0,15	3,06E-12	1,3319E-06	3,8827E-05	0,0001478	0,0001478 0,0002343 0,00020218	0,00020218
Δ pAi	0,2	3,22E-18	3,22E-18 9,1413E-10	9,0305E-08	5,733E-07	5,733E-07 9,6336E-07 5,733E-07	5,733E-07
∆ DAi	0,25	2,08E-20	2,2614E-13	6,2679E-11	5,873E-10	5,873E-10 8,7113E-10 2,5396E-10	2,5396E-10
∆ pAi	0,3	7,82E-25	2,152E-17	1,3261E-14	1,5189E-13	1,5189E-13	1,3261E-14
ΔpAi	0,35	1	7,9823E-22	,62E-29 7,9823E-22 8,4152E-19 9,1669E-18 4,2713E-18 5,5844E-20	9,1669E-18	4,2713E-18	5,5844E-20
Δ pAi	0,4	1,73E-34	1,1282E-26	1,524E-23	1,1488E-22		1,524E-23 1,1282E-26

#aff	200						
# non aff	200						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
∆ pAi	0,05	5,92E-06	0,03250945	0,09039173	0,13111935 0,15260313	0,15260313	0,15678006
ΔpAi	0,1	8,65E-11	7,4765E-05	0,00109084	0,00302686	0,00447365	0,00447365
A DA	0.15	8,02E-16	2,3653E-08	2,0257E-06	<u>ا</u> ت	,1771E-05 2,1573E-05	1,7772E-05
A DA	0.2	4.18E-21	1.5375E-12	6,7374E-10	7,764E-09	1,5417E-08	7,764E-09
A DAI	0.25	1	2,525E-17	4,4025E-14	8,5532E-13	1,4423E-12	2,8149E-13
A DAI	0.3		1.1488E-22	5,8424E-19	1,4886E-17	1,4886E-17	5,8424E-19
A DAI	0,35	۳	1,4784E-28	1,5457E-24	3,6958E-23	1,3394E-23	4,197E-26
ΔpAi	0,4	2,09E-45	5,2308E-35	7,6438E-31	ŀ	1,1224E-29 7,6438E-31	5,2308E-35

aff affected individuals

non affected Individuals

pAi non aff allele frequency in non affected individuals

Δ pAi % Difference in allele frequency between affected and non-affected individuals

Figure 3 (I)

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DISTRIBUTION p-VALUE

# aff	200						
# non aff	200						
	pAi non aff	0	1,0	0,2	0,3	0,4	0,5
ΔpAi	0,05	8E-13	0,00072323	0,00741965	0,0169842	0,0169842 0,02371865	0,02516449
∆ pAi	0,1	1,07E-24	3,7948E-10	2,4176E-07 2,7579E-06 6,9679E-06 6,9679E-06	2,7579E-06	6,9679E-06	6,9679E-06
∆ pAi	0,15	3,81E-37	1,0719E-18	5,8344E-14 4,2622E-12 1,8601E-11	4,2622E-12	1,8601E-11	1,1611E-11
∆ pAi	0,2	2,96E-50	5,0895E-29	1,6881E-22	6,9321E-20	6,9321E-20 3,7441E-19 6,9321E-20	6,9321E-20
ΔpAi	0,25	4,27E-64	0,25 4,27E-64 7,2043E-41	7,7528E-33	1,194E-29	1,194E-29 4,3462E-29	7,6438E-31
ΔpAi	0,3	9,7E-79	3,9328E-54	6,3017E-45	1,9429E-41		1,9429E-41 6,3017E-45
∆ pAi	0,35	0,35 2,91E-94	8,8513E-69	8,7879E-59 2,3478E-55	2,3478E-55	1,8839E-56	1,1206E-62
∆ pAi	0,4	9,5E-111	0,4 9,5E-111 7,7199E-85 1,8063E-74 1,4484E-71	1,8063E-74	1,4484E-71	1,8063E-74 7,7199E-85	7,7199E-85

#aff	150						
# non aff	850						
	pAi non aff	0	0,1	0,2	0,3	4,0	0,5
∆ pAi	0,05	0,05 2,16E-20	0,00994614	0,04896055	0,08358651	0,10417953	0,11025423
∆ pAi	0,1	2,01E-39	5,571E-07	0,00010149 0,00058665 0,00119145	0,00058665	0,00119145	0,00139743
∆ pAi	0,15	1,11E-58	2,7555E-13	8,462E-09	8,462E-09 2,9851E-07 1	1,2395E-06	1,6229E-06
∆ pAi	0,2	3,27E-78	2,1683E-21	3,2211E-14	1,1049E-11	1,111E-10	1,5638E-10
Δ pAi	0,25	4,96E-98	4,4952E-31	6,5226E-21 3,1015E-17 2,5169E-16	3,1015E-17	2,5169E-16	1,1763E-15
∆ pAi	6,0	3,7E-118	3,6987E-42	8,129E-29	6,9335E-24	6,9335E-24 5,4331E-22	6,5657E-22
ΔpAi	0,35	1,4E-138	1,6797E-54		1,2938E-31	1,2938E-31 2,9415E-29 2,5869E-29	2,5869E-29
Δ pAi	0,4	0,4 2,4E-159	5,4915E-68		2,1003E-40	4,8846E-48 2,1003E-40 1,3332E-37 6,8178E-38	6,8178E-38

non affected individuals affected individuals # non aff #aff

pAi non aff

aliele frequency in non affected individuals % Difference in allele frequency between affected and non-affected individuals

Figure 3 (II)



p-VALUE DISTRIBUTION

#aff	200						
# non aff	200		,				
	pAi non aff	0	1,0	0,2	6'0	0,4	0,5
∆ pAi	90'0	1,06E-12	0,00789803	0,05 1,06E-12 0,00789803 0,03942584 0,06867566 0,08621572	0,06867566	0,08621572	0,09083704
ΔpAi	0,1	3,45E-24	4,4217E-07	5,6883E-05	5,6883E-05 0,00031976	0,0006363	0,00070881
ΔpAi	0,15	5,9E-36	5,9E-36 4,3025E-13	•	3,3635E-09 9,2134E-08	3,319E-07	3,5871E-07
∆ pAi	0,2	0,2 4,73E-48	1,5566E-20	1,0346E-14	1,0346E-14 1,7218E-12	1,1512E-11	1,1512E-11 1,0047E-11
Δ pAi	0,25	1,67E-60	3,5436E-29	3,5436E-29 2,0473E-21 2,2178E-18	2,2178E-18	1,1498E-17	1,3524E-17
Δ pAi	6,0	2,46E-73	7,2498E-39	3,0748E-29 2,0601E-25 3,4525E-24	2,0601E-25	3,4525E-24	7,4807E-25
Δ pAi	0,35	1,44E-86	1,6945E-49	3,9559E-38	1,4118E-33	2,662E-32	1,4118E-33
ΔpAi	0,4	3,2E-100	3,2E-100 5,3051E-81	4,7325E-48 7,1282E-43 1,0691E-41	7,1282E-43	1,0691E-41	7,2652E-44

#aff	200						
# non aff	1000						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
∆ pAi	90'0	6,48E-24	5,7827E-05	0,00172627	0,00551541	0,00882876	0,00978249
∆ pAi	0,1	6,53E-47	3,065E-14	1,0301E-09	4,3205E-08	1,8833E-07	2,2731E-07
ΔpAi	0,15	1,2E-70	2,0716E-27	3,7441E-19	4,6626E-18	6,9719E-15	6,9719E-15
∆ pAi	0,2	3,33E-95	1,1636E-43	1,6614E-31	8,5632E-27	4,1421E-25	1,9885E-25
Δ pAi	0,25	1,2E-120	1,7683E-62	1,5329E-46	3,1722E-40	8,6765E-39	3,6071E-39
∆ pAi	0,3	5,3E-147	1,526E-83	4,2697E-64	2,5968E-56	3,9328E-54	2,5968E-56
Δ pAi	0,35	2,4E-174	1,184E-108	4,5658E-84	4,7426E-75	4,2624E-73	4,0958E-77
Δ pAi	0,4	9,4E-203	1,082E-131	082E-131 2,137E-106		1,8014E-96 3,3252E-95	6,725E-102

affected individuals #aff

non affected individuals # non aff

pAi non aff Δ pAi

allele frequency in non affected Individuals % Difference in allele frequency between affected and non-affected individuals

Figure 3 (III)



ALLELIC ASSOCIATION 3,000 MARKERS MAP

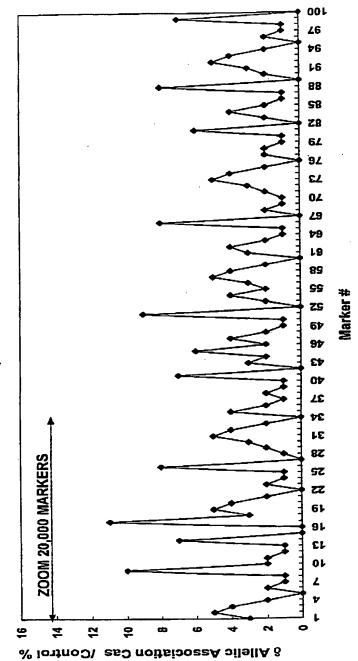


Figure 4



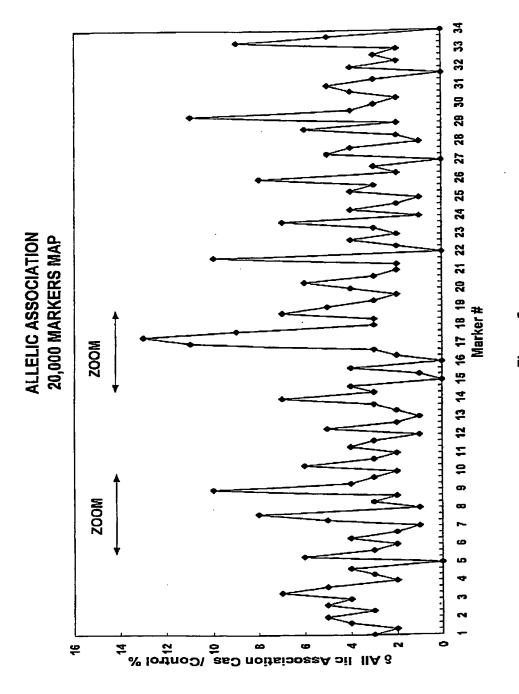


Figure 5



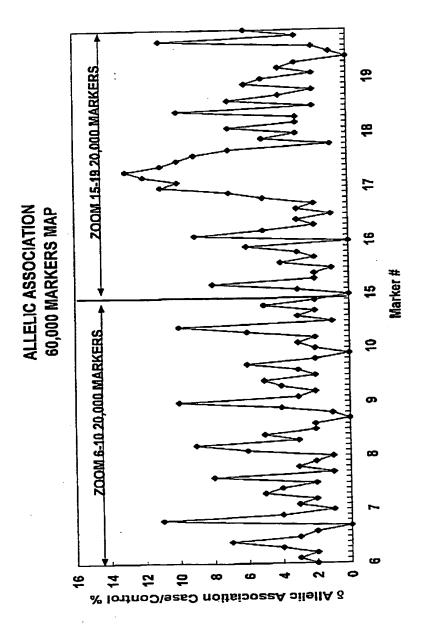


Figure 6



APO E REGION HAPLOTYPE FREQUENCY ANALYSIS

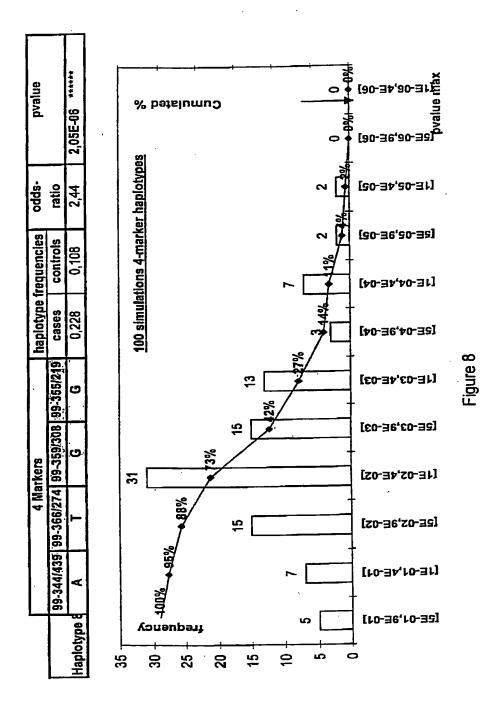
AD CONTROLS (248)	
AD CASES (225)	
POPULATIONS	

odds- P value	ratio	1,52 3,05E-03 ***	1,29 1,24E-01 *	1,36 2,83E-02 **	1,36 5,95E-02 **	,70 1,64E-02 **	19 3,59E-01	2,09 4,76E-05 ****	2.44 2.05E-08 *****
	ra	1,	-	<u> </u>	~		_	2,	6
haplotype frequencies	controls	908'0	0,165	0,306	0,209	0,071	0,129	0,122	0 40R
haplotype	cases	0,404	0,203	0,375	0,264	0,116	0,15	0,225	A 228
99-355	1,38E-01			g		⋖	∢	G	ď
99-359	6,63E-01		∢	മ	⋖			Ø	C
99-344	1,11E-01	ပ	တ			Ø			<
998-66	3,01E-01	ပ			ပ		ပ	 	1-
markers	p value	haplotype 1	haplotype 2	haplotype 3	haplotype 4	haplotype 5	haplotype 6	haplotype 7	D outolood

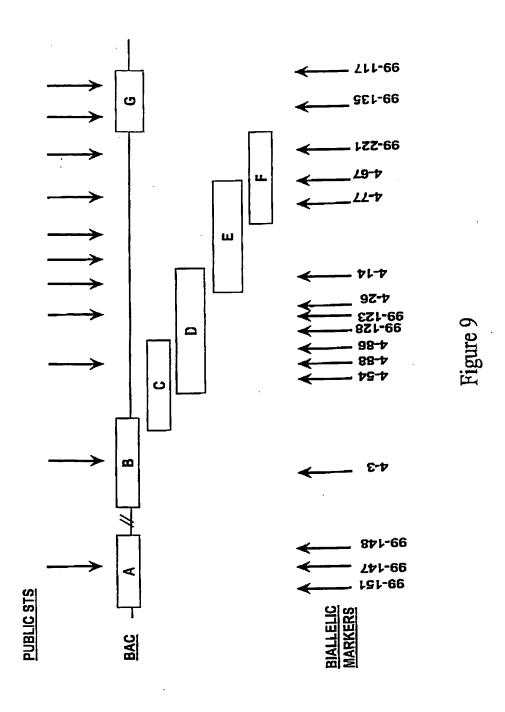
Figure 7



APO E REGION HAPLOTYPE SIMULATION POPULATION: 225 CASES vs 248 CONTROLS









PROSTATE CANCER ASSOCIATION STUDIES (FIRST SCREENING)

Sample size CASES = 112 CONTROLS=76 Population 35 sporadic cases > 65 years Characteristics + 77 familial cases	Population	PROSTATE CANCER	NON AFFECTED
35 sporadic cases + 77 familial cases	Sample size	CASES = 112	CONTROLS=76
+ 77 familial cases	Population	35 sporadic cases	> 65 years
	Characteristics	+ 77 familial cases	PSA<4

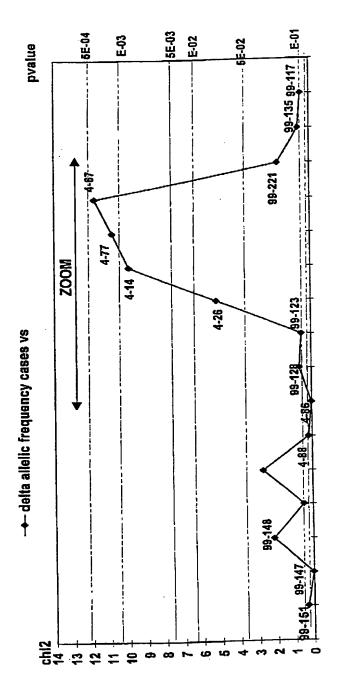
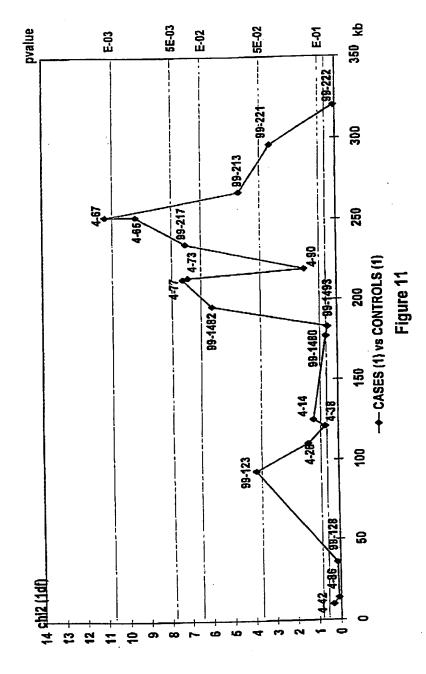


Figure 10



PROSTATE CANCER ASSOCIATION STUDIES (ZOOM)

	PROSTATE CANCER	NON-AFFECTED
	CASES (185)	CONTROLS (104)
characteristics	47 sporadic cases	> 65 years
of populations	+ 138 familial cases	PSA<4





PROSTATE CANCER HAPLOTYPE FREQUENCY ANALYSIS

	PROSTATE CANCER	NON-AFFECTED
	CASES (281)	CONTROLS (130)
characteristics	143 sporadic cases	> 65 years
of populations	+ 138 familial cases	PSA<4

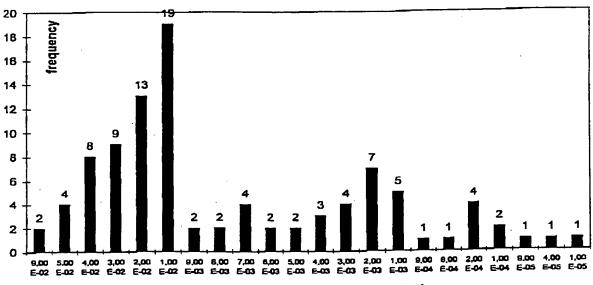
markera	99-123	426	4-14	4.77	99-217	4.67	99-213	99-221	99-135	ğg	haplotype		
bacs	H0287B09	8018	BO189E08			B0463F01			B0725B12	fredu	frequencies	relative	pvalue
RANGE					<	1	_					risk	
onica d	2 00F.01 1 00F-01 1 00E-	1 00F-01	1 00E-01	2.00E-02	01 2.00E-02 2.00E-02	6,00E-04	9,00E-02 7,00E-01 2,00E-01	7,00E-01	2,00E-01	CBBBS	controls		
P value		۵	C] [-	-	ပ	4	A	0,075	0,018	4,42	9,00E-04 ***
rapiotype o south	>	(⊲	י כ) C		· 1-	ပ	∢	<	0,095	0,016	6,46	6,00E-05 ****
napiotype / 200kb		(⊲	י כ) C	- ۱	· -	ပ	<		0,116	0,019	6,78	1,00E-05 ****
naplotype o < 100kb		c) C		- 1-		ပ	⋖		0,117	0,013	10,06	9,00E-07 *****
naplotype 3 < 17 1KB			•	. C	. 1-		ပ	⋖		0,117	0,025	5,17	2,00E-05 ****
napionype 4 <53Ku>)	. J-		ပ	< <		0,117	0,027	4,78	2,00E-05 ****
haplotype 3.1 <34KD>				ď		· —	ပ			0,222	0,109	2,33	4,00E-05 ****
napiotype 3.2 < 54Kb>) (-	-			_	0,251	0,134	2,17	2,00E-04 ****
napiotype 2.2 <38KD/)	. }-	· i	ပ			0,226	0,112	2,32	1,00E-04 ***
haplotype Z <32kD>					- 1	. +-				0,256	0,148	2,01	3,00E-04 ***
haplotype 1.1 <17 KD>					-	. 1-	ပ			0,233	0,129	2,05	6,00E-04 ***
haplotype 1.2 <15 Kb>													

Figure 12



PROSTATE CANCER HAPLOTYPE SIMULATIONS (100 ITERATIONS)

							1	haplotype f	requencies	relative	pvalue	Ì
ı	markers	4-14	4-77	99-217	4-67	99-213	99-221	cases	controls	risk		l
l	haplotype	С	G	T	T	G	Α	0,117	0,013	10,06	9,00E-07	ı



pvalue max of haplotypes for 100 simulations

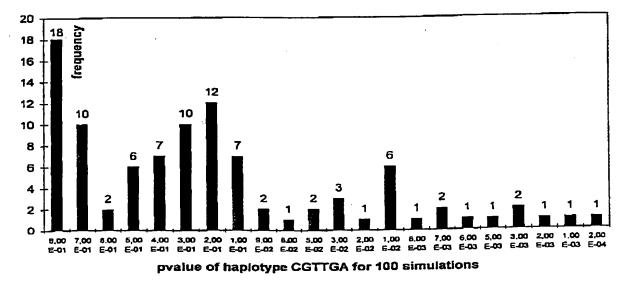


Figure 13



AVERAGE LD PATTERN GENOMIC HETEROGENEITY

Recombination rate	Lower	Higher	
	Α	В	
Nb markers	89	69	
All SNP	0.61 (749)	0.42 (1190)	
Rare < 0.2 Rare vs rare	0.75 (65)	0.17 (158)	
Frequent > 0.2 Frequent vs frequent	0.51 (410)	0.49 (544)	
Rare vs frequent	0.72 (274)	0.41 (488)	

FIGURE 14

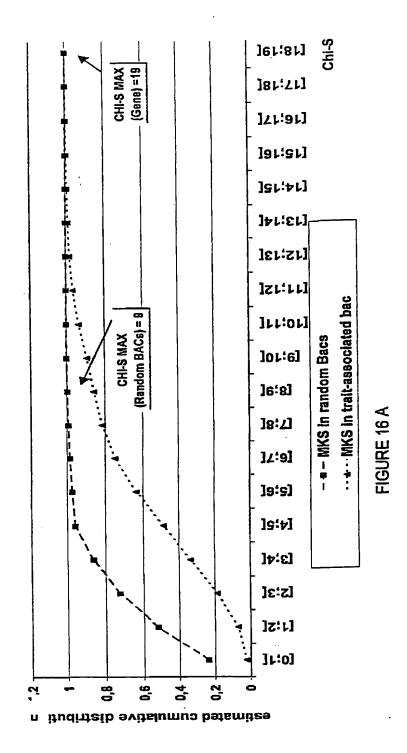


Exonic/nonexonic LD

	Nb pairs	Average intermarker distance	Average LD	
Exonic SNPs	36	26 kb	0.65±0.021	
Non exonic SNPs	60	36 kb	0.48±0.018	
Exonic/Non exonic	96	32 kb	0.60±0.015	

FIGURE 15







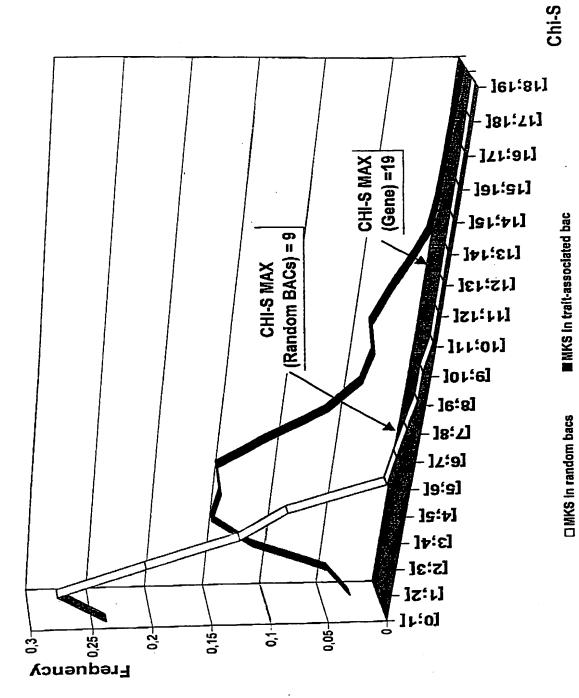
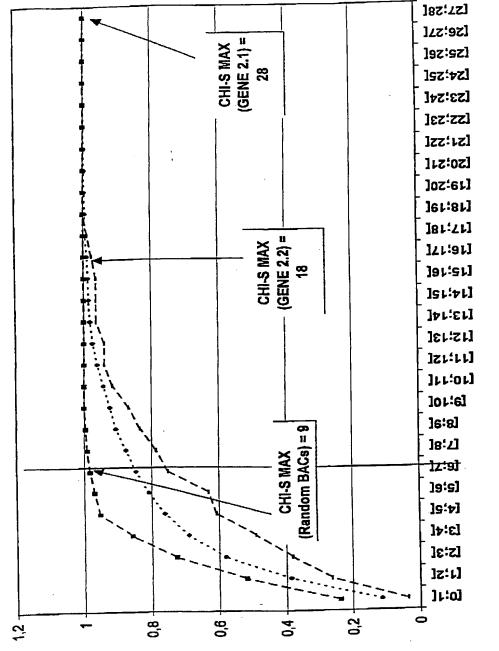


FIGURE 16B





Estimated cumulative distribution function

- • - MKS in random BACs
- • - MKS in BAC of GENE 2 (1:all mks)
- - - - MKS in BAC of GENE 2 (2: mks not desequilibrium)

FIGURE 17A



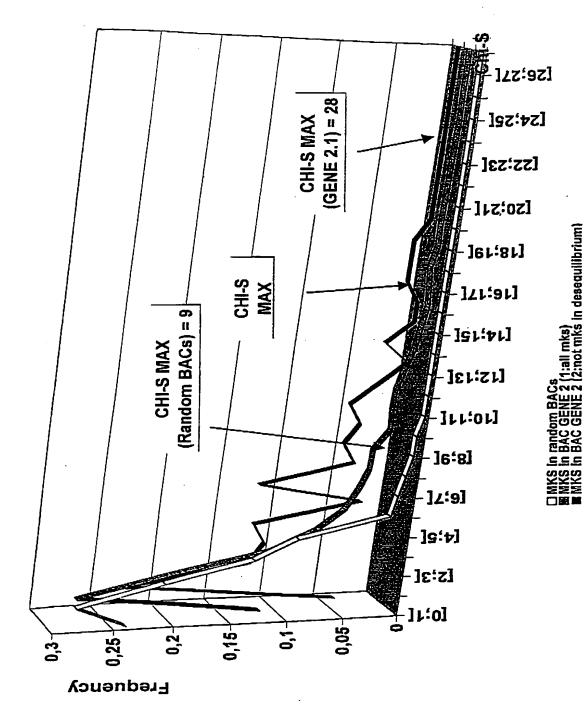
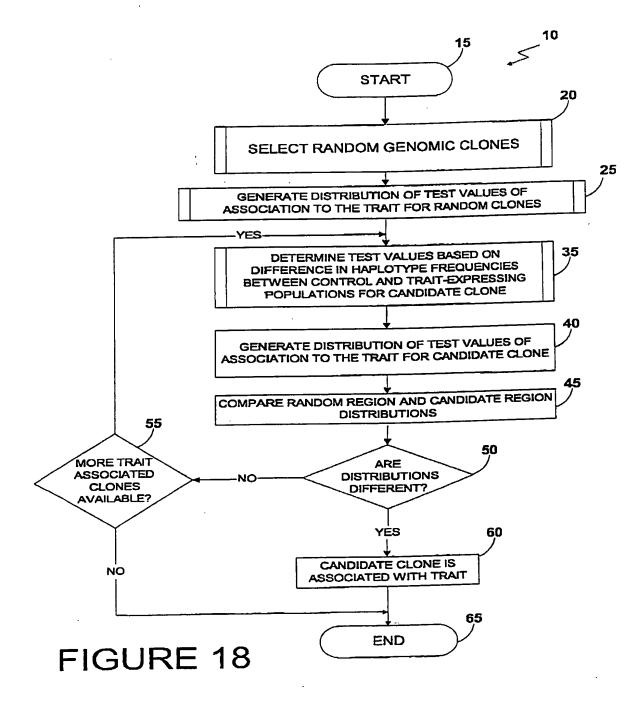
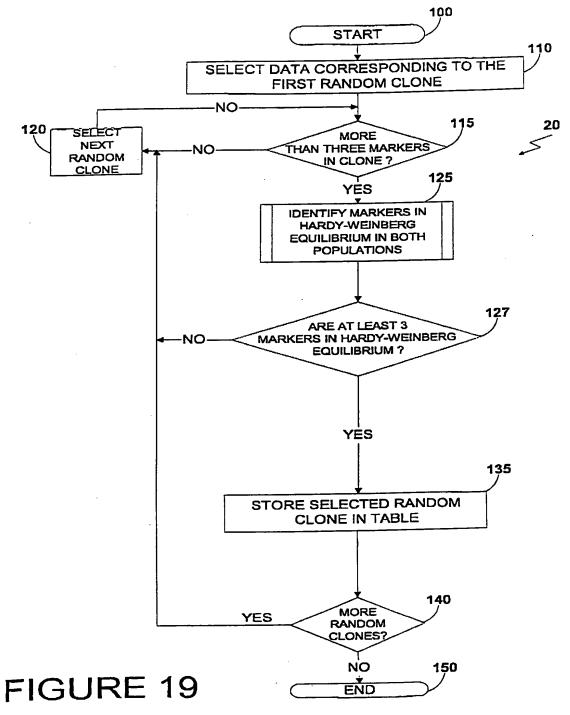


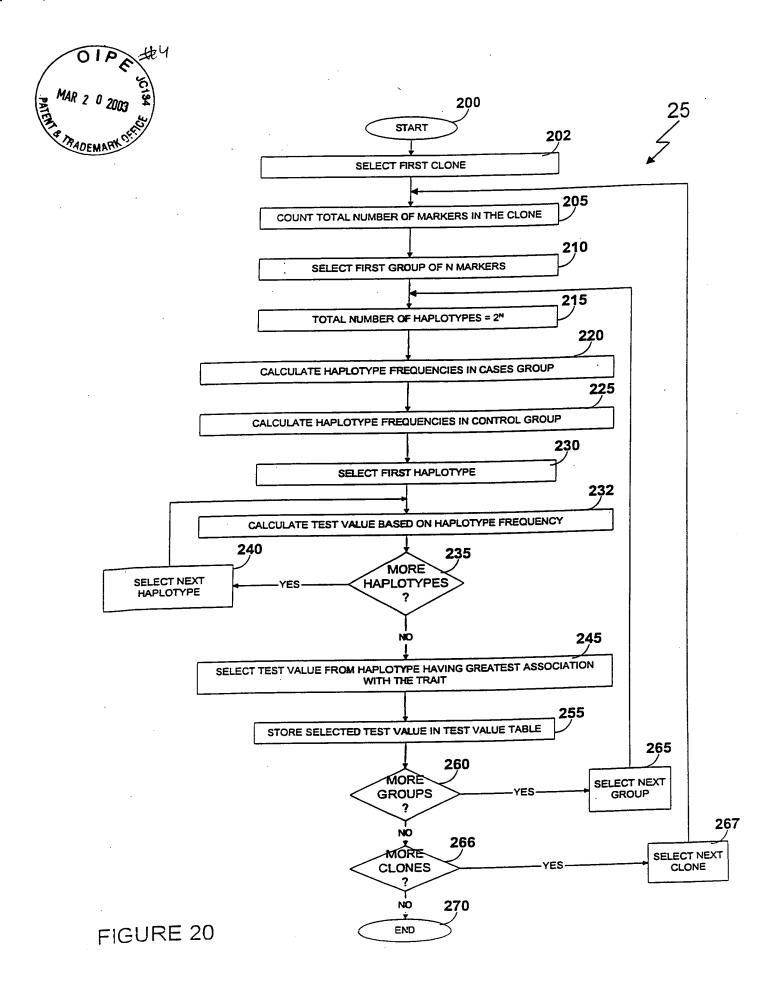
FIGURE 17 B



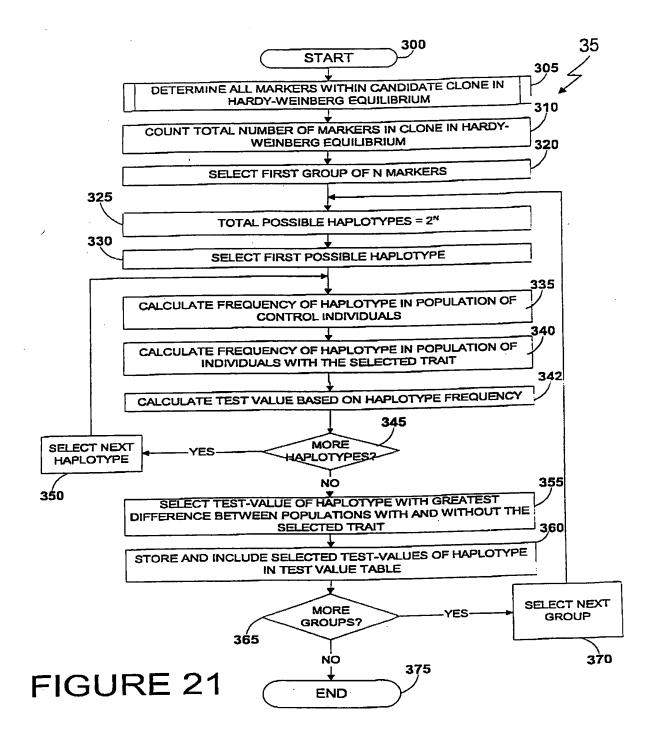














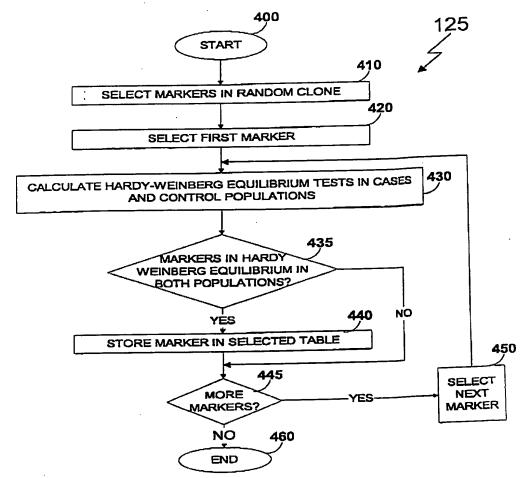


FIGURE 22



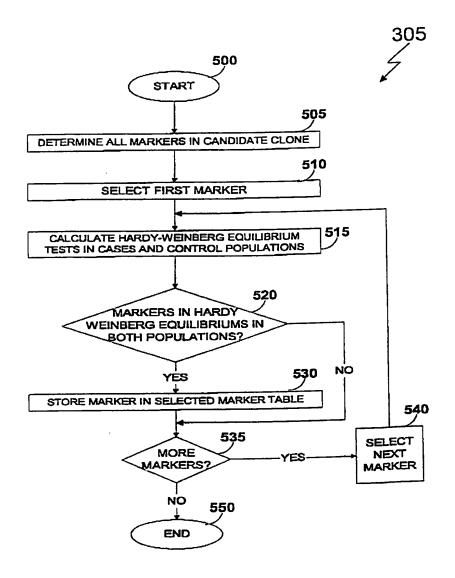


FIGURE 23



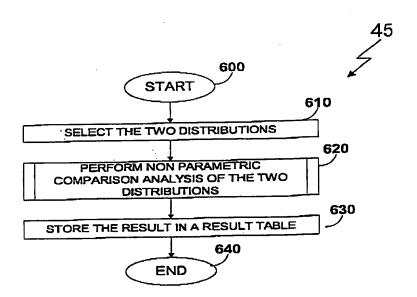


FIGURE 24



